Original Investigation

Efficacy of a House Dust Mite Sublingual Allergen Immunotherapy Tablet in Adults With Allergic Asthma
A Randomized Clinical Trial

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IMPORTANCE The house dust mite (HDM) sublingual allergen immunotherapy (SLIT) tablet is a potential novel treatment option for HDM allergy–related asthma.

OBJECTIVES To evaluate the efficacy and adverse events of the HDM SLIT tablet vs placebo for asthma exacerbations during an inhaled corticosteroid (ICS) reduction period.

DESIGN, SETTINGS, AND PARTICIPANTS Double-blind, randomized, placebo-controlled trial conducted between August 2011 and April 2013 in 109 European trial sites. The trial included 834 adults with HDM allergy–related asthma not well controlled by ICS or combination products, and with HDM allergy–related rhinitis. Key exclusion criteria were FEV_1 less than 70% of predicted value or hospitalization due to asthma within 3 months before randomization. Efficacy was assessed during the last 6 months of the trial when ICS was reduced by 50% for 3 months and then completely withdrawn for 3 months.

INTERVENTIONS 1:1:1 randomization to once-daily treatment with placebo (n = 277) or HDM SLIT tablet (dosage groups: 6 SQ-HDM [n = 275] or 12 SQ-HDM [n = 282]) in addition to ICS and the short-acting β_2-agonist salbutamol.

MAIN OUTCOMES AND MEASURES Primary outcome was time to first moderate or severe asthma exacerbation during the ICS reduction period. Secondary outcomes were deterioration in asthma symptoms, change in allergen-specific immunoglobulin G4 (IgG4), change in asthma control or asthma quality-of-life questionnaires, and adverse events.

RESULTS Among 834 randomized patients (mean age, 33 years [range, 17-83]; women, 48%), 693 completed the study. The 6 SQ-HDM and 12 SQ-HDM doses both significantly reduced the risk of a moderate or severe asthma exacerbation compared with placebo (hazard ratio [HR]: 0.72 [95% CI, 0.52-0.99] for the 6 SQ-HDM group, *P* = .045, and 0.69 [95% CI, 0.50-0.96] for the 12 SQ-HDM group, *P* = .03). The absolute risk differences based on the observed data (full analysis set) in the active groups vs the placebo group were 0.09 (95% CI, 0.01-0.15) for the 6 SQ-HDM group and 0.10 (95% CI, 0.02-0.16) for the 12 SQ-HDM group. There was no significant difference between the 2 active groups. Compared with placebo, there was a reduced risk of an exacerbation with deterioration in asthma symptoms (HR, 0.72 [95% CI, 0.49-1.02] for the 6 SQ-HDM group, *P* = .11, and 0.64 [95% CI, 0.42-0.96] for the 12 SQ-HDM group, *P* = .03) and a significant increase in allergen-specific IgG4. However, there was no significant difference for change in asthma control questionnaire or asthma quality-of-life questionnaire for either dose. There were no reports of severe systemic allergic reactions. The most frequent adverse events were mild to moderate oral pruritus (13% for the 6 SQ-HDM group, 20% for the 12 SQ-HDM group, and 3% for the placebo group), mouth edema, and throat irritation.

CONCLUSIONS AND RELEVANCE Among adults with HDM allergy–related asthma not well controlled by ICS, the addition of HDM SLIT to maintenance medications improved time to first moderate or severe asthma exacerbation during ICS reduction, with an estimated absolute reduction at 6 months of 9 to 10 percentage points; the reduction was primarily due to an effect on moderate exacerbations. Treatment-related adverse events were common at both active doses. Further studies are needed to assess long-term efficacy and safety.

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Bronchial asthma is a serious global health problem with increasing prevalence in many countries.[1] House dust mite (HDM) sensitization is present in up to 50% of patients with asthma,[2] and exposure to HDM allergen has been related to asthma severity.[3]

Persistent symptoms are common in many patients with HDM allergic disease.[4] Treatment options include inhaled corticosteroids (ICS) and long-acting β-agonists, but up to 30% of patients remain symptomatic, uncontrolled, or both despite treatment.[5] Uncontrolled asthma is identified as a major risk factor for future exacerbations and poorer clinical outcomes.[6]

HDM *house dust mite*
FAS *full analysis set*
ICS *inhaled corticosteroid(s)*
MID *minimal important difference*
SABA *short-acting β_2-agonist*
SLIT *sublingual allergen immunotherapy*

Allergen immunotherapy is the only treatment option for allergic disease with evidence of a disease-modifying effect[7] and thus a potential for sustained benefits when therapy is terminated.

Allergen immunotherapy has been shown to be effective in the treatment of allergic rhinitis due to airborne allergens, including HDM allergen.[8,9] Allergen immunotherapy improves symptoms and reduces medication scores both during treatment and following treatment cessation[7,10] and has been shown to prevent the development of asthma.[11]

Previously, the HDM sublingual allergen immunotherapy (SLIT) tablet has proven to be effective in reducing the requirement for ICS[12,13] and in reducing allergic rhinitis symptoms and need for pharmacotherapy[9,14,15] among patients with HDM respiratory allergic disease. However, to our knowledge, the effect on risk of asthma exacerbations has not been addressed previously.

This trial investigated the efficacy of the HDM SLIT tablet among participants with HDM allergy–related asthma, not well controlled by ICS, and with HDM allergy–related rhinitis. The primary objective of the trial was to evaluate the efficacy of the HDM SLIT tablet in 2 different doses (6 SQ-HDM and 12 SQ-HDM) vs placebo, measured by reducing the risk for an asthma exacerbation during a 6-month ICS reduction period.

Methods

The trial protocol (Supplement 1) and amendments were approved by the relevant ethics committees and institutional review boards. The trial was a randomized, double-blind, parallel group, placebo-controlled trial, designed and conducted in accordance with the principles of the Declaration of Helsinki (adopted in 1964, and its amendments and subsequent clarifications[16]) and in compliance with the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use's (ICH's) Good Clinical Practice guidelines.[17] Written informed consent was obtained from all participants.

The HDM SLIT tablet contains extract from 2 species of cultivated HDM (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), produced in a standardized process with a 1:1:1:1 ratio of the major allergens (Group 1 allergens of *D farinae* and *D pteronyssinus* and Group 2 allergens of *D farinae* and *D pteronyssinus*), and formulated as a rapidly dissolving oral lyophilisate for sublingual administration (ALK). The biological activity of the HDM SLIT tablet is related to the activity of the allergens and is expressed in the unit SQ-HDM. The placebo and active products were similar in appearance, smell, and taste. One tablet per day was to be placed under the tongue, preferably in the morning. Eating and drinking was not allowed for 5 minutes. The maximum duration of treatment with the SLIT tablet was 18 months.

Randomization was performed in blocks of 6 by the sponsor using the SAS system for Windows (SAS Institute), version 9.3, which generates random assignment of treatment groups to randomization numbers. Further details are provided in Supplement 2.

The trial was conducted at 109 sites in 13 European countries from August 11, 2011, through April 24, 2013. The participants were randomized (1:1:1) to receive placebo, the 6 SQ-HDM tablets, or the 12 SQ-HDM tablets, as add-on therapy to ICS and short-acting β_2-agonists (SABA). Eligible patients were adults with a positive result for the HDM-specific serum immunoglobulin E (IgE) and skin prick test; a clinical history of more than 1 year of allergic asthma and allergic rhinitis with HDM being considered clinically as a major trigger, not well controlled by ICS (equivalent to budesonide, 400-1200 µg) at inclusion; and a forced expiratory volume in the first second of expiration (FEV_1) at randomization of 70% or more of predicted value. The Asthma Control Questionnaire (ACQ) score[18] required for randomization had to be from 1 through 1.5 (score range, 0-6; values below 1 = controlled asthma, values above 1.5 = uncontrolled asthma). Hospitalization due to an asthma exacerbation within 3 months prior to randomization was an exclusion criterion. Participants could have multiple sensitizations but were not allowed to have a relevant clinical history of perennial allergic asthma or rhinitis caused by other allergens. As part of the baseline data collection, site staff collected data on demographic characteristics, including race and ethnicity ascertained by multiple choices (Caucasian, Asian, African, Hispanic, or other [with room for specification]). Information on race and ethnicity was collected because it was recommended by the US Food and Drug Administration and ICH guidance (E5[R1], Ethnic Factors in the Acceptability of Foreign Clinical Data) that sponsors collect ethnicity data in clinical trials to assist in assessing the relevance of foreign study population data to US populations and be able to bridge data to new regions. Further details are listed in Supplement 2.

The trial design is shown in eFigure 1 in Supplement 2. Period 1 included screening and switching of all participants from their regular ICS asthma controller to budesonide and SABA. Diary recordings of the last 2 weeks of period 1 served as participant's individual baseline. From randomization and throughout period 2, the participants received their assigned intervention in addition to ICS and SABA. The duration of the period varied from 7 to 12 months depending on the time of inclusion because period 2 had a fixed stop date in October.

During the last approximately 4 weeks of period 2, the participant started filling in the electronic diary and recorded asthma symptoms, medication use, and lung function twice daily. Efficacy was primarily assessed during the ICS reduction and withdrawal period (period 3) that began in October 2012 and covered the last 6 months of the treatment period. Daily ICS use was reduced to 50% for 3 months and subsequently withdrawn completely for participants who did not experience an asthma exacerbation. The primary end point, time to first moderate or severe asthma exacerbation (defined below), was measured from the start of period 3 until the time of the first asthma exacerbation.

An asthma exacerbation was defined according to the American Thoracic Society and European Respiratory Society (ATS/ERS) recommendation[19,20]; and in practice described by 1 or more of the following criteria for moderate or severe asthma exacerbation leading to a change in treatment.

Criteria for a moderate asthma exacerbation included (1) nocturnal awakening(s) due to asthma requiring SABA use for at least 2 consecutive nights or an increase of at least 0.75 points in daily symptom score from baseline value on at least 2 consecutive days; (2) an increase from baseline in SABA use on at least 2 consecutive days (a minimum increase of 4 puffs per day); (3) a 20% or more decrease in peak expiratory flow from baseline on at least 2 consecutive mornings or evenings or a 20% or more decrease in FEV_1 from baseline; and (4) a visit to the emergency department or an unscheduled visit to the trial site for asthma treatment not requiring systemic corticosteroids.

Criteria for a severe asthma exacerbation included (1) a requirement for systemic corticosteroids for the treatment of asthma symptoms for at least 3 days; and (2) an emergency department visit due to asthma requiring systemic corticosteroids, or a hospitalization for more than 12 hours due to asthma.

Baseline values were defined as the mean values for each individual participant during the last 14 days of the screening period.

Key secondary end points included time to first asthma exacerbation from the start of the ICS reduction and withdrawal period (period 3) with deterioration in asthma symptoms and nocturnal awakenings; changes from baseline in HDM-specific immunoglobulin G4 (IgG4); and the proportion of participants with a minimal important difference (MID; defined as change >0.5) in ACQ or standardized Asthma Quality of Life Questionnaire (AQLQ[S]) score without an increased dose of ICS, or with no MID in ACQ or AQLQ(S) score despite lower ICS usage at the end of trial (third and fourth key secondary end points). Of the 17 prespecified exploratory end points, this article reports the following 3 that are related to the primary end point: (1) time to first asthma exacerbation from the start of period 3 with an increased use of SABA; (2) the time to the first asthma exacerbation from the start of period 3 with deterioration in lung function; and (3) time to the first severe asthma exacerbation from the start of period 3.

Safety assessments included adverse events reporting, findings on physical examinations, vital signs, lung function measurements (peak expiratory flow and FEV_1), and clinical safety laboratory assessments (details listed in Supplement 2). Adverse events were coded using MedDRA (ICH), version 15.0.

Statistics

The principal statistical software used was SAS (SAS Institute), version 9.3. Details of the sample size calculation and statistical methodology are provided in Supplement 2 and in the statistical analysis plan (Supplement 1).

In brief, the power calculation was based on the assumption that about 65% of participants in the placebo group would experience an asthma exacerbation. The assumption was based on a small ICS withdrawal trial, in which loss of asthma control developed in 8 of 12 placebo-treated patients over the 10-week period of ICS withdrawal.[21] A reduction in the rate of first asthma exacerbation of approximately 30%, corresponding to a hazard ratio (HR) of 0.70, was considered clinically relevant. Accordingly, it was estimated that 266 participants per treatment group would provide at least an 80% power to detect a difference between HDM SLIT tablet and placebo in the time to first asthma exacerbation corresponding to an HR of 0.70 at the 5% significance level (including an expected dropout of about 10%).

The full analysis set (FAS) included all randomized participants in accordance with the ICH intention-to-treat principle. The primary analysis was based on the FAS with multiple imputations (FAS-MI) of missing data. All other analyses were based on the FAS.

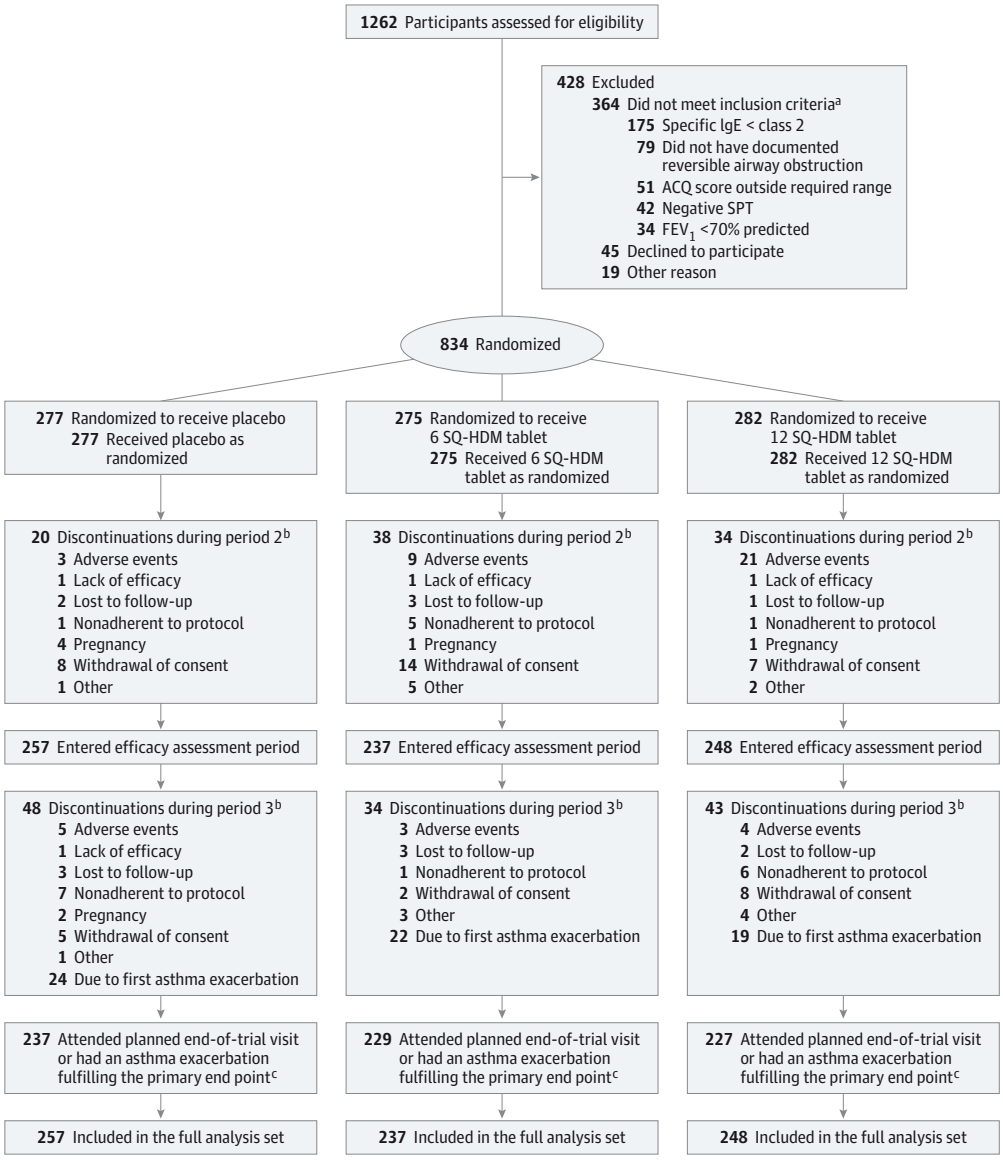
The primary efficacy analysis of time to first moderate or severe asthma exacerbation was performed with a Cox proportional hazards regression analysis stratified for country. Multiplicity was controlled by a prespecified hypothesis test strategy. The first hypothesis to be tested was the hypothesis that all 3 groups were equal, controlled by Fisher least significant difference procedure.[22] This procedure preserves the experimentwise type I error rate at the nominal level of significance in case of 3 treatment groups. Time to the first asthma exacerbation by individual criteria was analyzed similarly to the primary efficacy end point. Log-transformed IgG4 at the end of the trial was analyzed with a linear mixed-effect model. Analyses of the odds for improvement (defined as a 0.5 points change from baseline[23,24]) in ACQ or AQLQ(S) score controlled for ICS was performed with a logistic regression analysis. The 4 key secondary hypotheses were tested in hierarchical order, first for the comparison of the 12 SQ-HDM group with the placebo group and then for the 6 SQ-HDM group with the placebo group. The procedure continued if a hypothesis was rejected ($P < .05$). Other secondary analyses were considered supportive in nature and were not controlled for multiplicity.

Safety data were reported by descriptive statistics only. All analyses were 2-sided and tested at a 5% significance level.

Results

A total of 834 participants were randomized to receive the 6 SQ-HDM tablets (n = 275), 12 SQ-HDM tablets (n = 282) or placebo (n = 277). Participant characteristics through the entire trial are summarized in **Figure 1**. Across treatments groups, the

Figure 1. Participant Disposition Throughout the Trial



ACQ indicates Asthma Control Questionnaire; FEV_1, forced expiratory volume in the first second of expiration; ICS, inhaled corticosteroids; IgE, immunoglobulin E; SPT, skin prick test. The biological activity of the house dust mite sublingual allergen immunotherapy tablet is related to the activity of the allergens and is expressed in the unit SQ-HDM.

[a] More than 1 criterion could apply to each individual.

[b] Period 2, in which participants received the intervention as an add-on to ICS, lasted 7 to 12 months; period 3, in which participants began ICS reduction/withdrawal, lasted 6 months.

[c] The protocol defined that, following an asthma exacerbation, participants were offered to continue in the trial at an adjusted ICS dose and provide data to secondary end points. The participants discontinuing the trial following an exacerbation were considered to have completed the trial (26 participants in the 6 SQ-HDM group, 22 in the 12 SQ-HDM group, and 28 in the placebo group).

number of dropouts were comparable (6 SQ-HDM group, 72 participants [26%]; 12 SQ-HDM group, 77 participants [27%]; placebo group, 68 participants [25%]). The main reasons for trial discontinuations were asthma exacerbations during the ICS reduction period (ie, after meeting the primary end point), adverse events and withdrawals of consent. The number of discontinuations due to adverse events was numerically higher in the 12 SQ-HDM group (n = 25) whereas the number of discontinuations following an asthma exacerbation was higher in the placebo group (n = 24) (Figure 1).

Additional characteristics and disease-specific baseline values are listed in **Table 1.** There were no major differences between the 3 groups. The overall mean duration of allergic asthma was 13 years (SD, 11 years). Approximately one-third of the population was monosensitized to HDM, whereas one-third had 3 or more additional allergen sensitizations. The mean daily ICS use at randomization was 588 µg of budesonide (SD, 252 µg), and this level remained stable throughout the maintenance phase (period 2) of the trial, with no difference in ICS use between groups at the start of the efficacy assessment

Table 1. Participant Demographics and Asthma Characteristics at Baseline

	Treatment Group			
	Placebo (n = 277)	6 SQ-HDM Tablet (n = 275)[a]	12 SQ-HDM Tablet (n = 282)[a]	Overall (N = 834)
Participant Demographics				
Sex, No. (%)				
Men	151 (55)	133 (48)	147 (52)	431 (52)
Women	126 (45)	142 (52)	135 (48)	403 (48)
Ethnic origin, No. (%)				
Caucasian	273 (99)	272 (99)	277 (98)	822 (99)
Asian	1 (<1)	1 (<1)	2 (<1)	4 (<1)
African	1 (<1)	1 (<1)	2 (<1)	4 (<1)
Hispanic	2 (<1)	0	1 (<1)	3 (<1)
Other	0	1 (<1)	0	1 (<1)
Smoking history, No. (%)				
Nonsmoker	214 (77)	198 (72)	214 (76)	626 (75)
Previous smoker	36 (13)	50 (18)	38 (13)	124 (15)
Smoker	27 (10)	27 (10)	30 (11)	84 (10)
Sensitization status, No. (%)[b]				
Only HDM	102 (37)	90 (33)	91 (32)	283 (34)
1 other than HDM	44 (16)	51 (19)	45 (16)	140 (17)
2 others than HDM	41 (15)	37 (13)	48 (17)	126 (15)
≥3 others than HDM	90 (32)	97 (35)	98 (35)	285 (34)
Age, mean (SD), y	33.0 (12.2)	33.6 (11.3)	33.7 (11.6)	33.4 (11.7)
Median (range)	30 (18.0-83.0)	32 (18.0-75.0)	32 (17.0-74.0)	31 (17.0-83.0)
Weight, mean (SD), kg	76.3 (16.7)	76.5 (16.4)	75.9 (16.3)	76.2 (16.4)
Median (range)	76 (42.0-145.5)	76 (45.0-118.0)	74 (45.0-125.0)	75 (42.0-145.5)
Height, mean (SD), cm	172.8 (10.5)	171.2 (9.5)	171.6 (9.4)	171.9 (9.8)
Median (range)	173 (151.0-200.0)	171 (150.0-198.0)	172 (150.0-197.0)	172 (150.0-200.0)
BMI, mean (SD)	25.5 (5.0)	26.0 (4.8)	25.7 (4.7)	25.7 (4.8)
Median (range)	24.7 (16.4-54.0)	25.3 (17.0-40.2)	25.1 (17.4-44.0)	25.0 (16.4-54.0)
Participant Asthma Characteristics				
Average morning PEF, mean (SD), L/min	456 (132)	433 (124)	443 (125)	444 (127)
Median (range)	451 (171-827)	418 (104-758)	418 (179-805)	425 (104-827)
Average diurnal variability in PEF, mean (SD), %	8.50 (4.70)	9.05 (5.94)	8.29 (5.19)	8.61 (5.30)
Median (range)	7.43 (2.04-32.80)	7.36 (2.07-40.28)	6.98 (0.90-29.65)	7.23 (0.90-40.28)
FEV_1 at randomization, L				
Mean (SD)	3.52 (0.89)	3.33 (0.79)	3.33 (0.82)	3.39 (0.84)
Median (range)	3.41 (1.62-6.35)	3.23 (1.81-5.92)	3.24 (1.67-5.57)	3.29 (1.62-6.35)
FEV_1, % of predicted value, mean (SD)	94.34 (13.79)	92.32 (12.66)	91.39 (12.91)	92.67 (13.17)
Median (range)	92.8 (68.0-134.4)	90.6 (63.4-127.0)	90.9 (69.5-131.6)	91.1 (63.4-134.4)
ACQ at randomization[c]	1.22 (0.18)	1.24 (0.17)	1.23 (0.17)	1.23 (0.17)
Median (range)	1.17 (0.86-2.00)	1.29 (0.86-1.71)	1.29 (0.71-1.57)	1.29 (0.71-2.00)
AQLQ(S) score at randomization, mean (SD)	5.54 (0.78)	5.46 (0.88)	5.49 (0.78)	5.50 (0.81)
Median (range)	5.61 (2.19-6.97)	5.63 (1.22-6.84)	5.56 (2.44-6.88)	5.59 (1.22-6.97)
ICS at randomization, mean (SD), µg of budesonide/d	580 (246)	582 (246)	602 (264)	588 (252)
Median (range)	400 (400-1200)	400 (200-1200)	400 (200-1200)	400 (200-1200)
Total asthma daytime symptom score, mean (SD)[d]	2.63 (2.05)	2.73 (1.98)	2.58 (1.92)	2.64 (1.98)
Median (range)	2.14 (0.00-12.00)	2.46 (0.00-10.36)	2.31 (0.00-8.93)	2.31 (0.00-12.00)
Asthma nocturnal symptom score, mean (SD)	0.61 (0.56)	0.64 (0.54)	0.57 (0.50)	0.61 (0.53)
Median (range)	0.46 (0.00-2.86)	0.57 (0.00-2.25)	0.50 (0.00-2.14)	0.50 (0.00-2.86)

(continued)

Table 1. Participant Demographics and Asthma Characteristics at Baseline (continued)

	Treatment Group			
	Placebo (n = 277)	6 SQ-HDM Tablet (n = 275)[a]	12 SQ-HDM Tablet (n = 282)[a]	Overall (N = 834)
Nocturnal awakening requiring SABA intake, mean (SD)[e]	0.12 (0.26)	0.12 (0.23)	0.11 (0.23)	0.12 (0.24)
Median (range)	0 (0.00-1.00)	0 (0.00-1.00)	0 (0.00-1.00)	0 (0.00-1.00)
24-h SABA intake, mean (SD), No. of 200-µg puffs	1.30 (1.53)	1.42 (1.87)	1.23 (1.47)	1.32 (1.63)
Median (range)	0.82 (0.00-11.14)	0.85 (0.00-14.25)	0.67 (0.00-7.38)	0.77 (0.00-14.25)
IgG4, mean (SD), mg_A/L				
Dermatophagoides pteronyssinus	0.5 (0.5)	0.4 (0.4)	0.4 (0.6)	0.4 (0.5)
Median (range)	0.3 (0.0-3.4)	0.3 (0.0-3.3)	0.3 (0.0-6.4)	0.3 (0.0-6.4)
Dermatophagoides farinae	0.4 (0.5)	0.4 (0.3)	0.5 (0.9)	0.4 (0.6)
Median (range)	0.3 (0.0-3.7)	0.3 (0.0-2.7)	0.2 (0.0-9.8)	0.3 (0.0-9.8)

Abbreviations: ACQ, asthma control questionnaire; AQLQ(S), asthma quality of life questionnaire (standardized); BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FEV_1, forced expiratory volume in the first second of expiration; ICS, inhaled corticosteroid; IgG4, immunoglobulin G4; mgA/L, milligram antigen-specific antibodies per liter; PEF, peak expiratory flow; SABA, short-acting β_2-agonist.

[a] The biological activity of the house dust mite sublingual allergen immunotherapy tablet is related to the activity of the allergens and is expressed in the unit SQ-HDM.

[b] The most common cosensitizations by skin prick test were cat (43% positive) and grass (41% positive).

[c] Asthma nocturnal symptom score: range, 0 to 3; worst asthma symptom (wheezing, coughing, shortness of breath, or chest tightness) during the night on a 0 to 3 scale (0 indicated no symptoms, 3 indicated severe symptoms).

[d] Asthma daytime symptom score: range 0 to 12; sum of severity of each asthma symptom (wheezing, coughing, shortness of breath and chest tightness, and exercise induced symptoms) during the day on a 0 to 3 scale (0 indicated no symptoms, 3 indicated severe symptoms).

[e] For each participant the mean number of nocturnal awakenings with SABA intake over the 14-day baseline period.

period. Approximately 40% of the participants used 800 µg to 1200 µg of budesonide per day at randomization. At randomization, mean asthma control score (as determined by ACQ) was 1.24 (0.17) for the 6 SQ-HDM group, 1.23 (0.17) for the 12 SQ-HDM group, and 1.22 (0.18) for the placebo group. A prespecified evaluation of the Global Initiative for Asthma (GINA) asthma control level (according to an algorithm previously described)[25] showed that overall 72% of participants had partly controlled asthma and 28% of participants had uncontrolled asthma at randomization. The main reasons for being uncontrolled according to GINA criteria were nocturnal awakenings and activity limitations in combination with daytime symptoms, an FEV_1 below 80% of predicted value, or need for SABA use. At the start of period 3 when ICS was reduced, the mean participant ACQ score was 0.98 for the 6 SQ-HDM group, and 0.93 for the 12 SQ-HDM group, and 1.01 for the placebo group. Compliance to treatment was 94% with no differences between groups.

The primary efficacy results for time to the first asthma exacerbation are shown in **Table 2**. At the end of the 6-month efficacy assessment period, 6 SQ-HDM and 12 SQ-HDM tablets significantly reduced the risk of a moderate or severe asthma exacerbation compared with placebo (HR for the FAS-MI: 0.72 [95% CI, 0.52-0.99] for the 6 SQ-HDM group, $P = .045$, and 0.69 [95% CI, 0.50-0.96] for the 12 SQ-HDM group, $P = .03$; Kaplan-Meier–estimated absolute risk for first exacerbation for the FAS: 0.24 (n = 62) for the 6 SQ-HDM group, 0.24 (n = 59) for the 12 SQ-HDM group, and 0.33 (n = 83) for the placebo group; risk difference vs placebo: 0.09 [95% CI, 0.01-0.15] for the 6 SQ-HDM group and 0.10 [95% CI, 0.02-0.16] for the 12 SQ-HDM group). However, there was no significant difference between the 2 active groups (HR, 0.96 [95% CI, 0.68-1.37], $P = .84$).

The proportions of participants with a moderate or severe asthma exacerbation for the FAS are shown in **Figure 2**.

There were no statistically significant interactions between treatment and any prespecified subgroup variable (sex, allergen sensitization type, other indoor sensitizations, or age group) (Supplement 2).

The prespecified secondary analyses of time to first asthma exacerbation for the individual criteria are displayed in Table 2. For the 12 SQ-HDM group, there was a statistically significant and clinically relevant reduction in the HR for a moderate asthma exacerbation with deterioration in asthma symptoms or nocturnal awakenings of 0.64 [0.42-0.96] (first key secondary end point), for a moderate asthma exacerbation with deterioration in lung function of 0.58 [0.36-0.93], and for a moderate asthma exacerbation with increased SABA use of 0.52 [0.29-0.94] (exploratory end points). For the 6 SQ-HDM group, only time to first asthma exacerbation with deterioration in lung function was statistically significantly different from placebo (HR, 0.60 [0.38-0.95]; $P = .030$) (Table 2). The exploratory analysis of time to first severe asthma exacerbation showed no statistically significant reductions (HR: 0.79 [0.40-1.55] for the 6 SQ-HDM group, $P = .49$, and 0.49 [0.23-1.08] for the 12 SQ-HDM group, $P = .08$).

The HDM SLIT tablet groups experienced dose-dependent increases in allergen-specific IgG4 (to *D pteronyssinus* and *D farinae*) (Table 2) (second key secondary outcome). The between-group differences for both active groups vs placebo were statistically significant from week 4 and onwards (eFigure 2 in Supplement 2). At the end of trial, the between-group difference in log10-transformed IgG4 to *D pteronyssinus* for the 6 SQ-HDM group vs placebo group was 0.461 (0.417-0.505), $P < .001$, and 0.595 (0.546-0.643) for the 12 SQ-HDM group vs placebo, $P < .001$.

Table 2. Overview of Primary, Key Secondary, and Exploratory End Point Efficacy Results for Each Treatment Group

End Point	Total Participants	No. of Participants With Event	Treatment Effect	
			HR (95% CI)	*P* Value
Primary End Point				
Time to first asthma exacerbation from the start of period 3[a]				
FAS-MI[b]				
Placebo group	277	NA[c]	Reference	
6 SQ-HDM group	275	NA[c]	0.72 (0.52 to 0.99)	.045
12 SQ-HDM group	282	NA[c]	0.69 (0.50 to 0.96)	.03
FAS				
Placebo group	257	83 (32)	Reference	
6 SQ-HDM group	237	62 (26)	0.69 (0.49 to 0.96)[d]	.03
12 SQ-HDM group	248	59 (24)	0.66 (0.47 to 0.93)[d]	.02
Key Secondary End Points				
Time to first asthma exacerbation with deterioration in asthma symptoms or nocturnal awakenings				
Placebo group	257	57 (22)	Reference	
6 SQ-HDM group	237	45 (19)	0.72 (0.49 to 1.07)	.17
12 SQ-HDM group	248	39 (16)	0.64 (0.42 to 0.96)	.03
Change from baseline to end of trial in log10-transformed IgG4				
Dermatophagoides pteronyssinus				
Placebo group	235	Mean (SD): −0.037 (0.014)	Reference	
6 SQ-HDM group	217	Mean (SD): 0.425 (0.022)	MD (95% CI): 0.461 (0.417 to 0.505)	<.001
12 SQ-HDM group	226	Mean (SD): 0.558 (0.024)	MD (95% CI): 0.595 (0.546 to 0.643)	<.001
Dermatophagoides farinae				
Placebo group	235	Mean (SD): −0.054 (0.015)	Reference	
6 SQ-HDM group	217	Mean (SD): 0.404 (0.022)	MD (95% CI): 0.458 (0.413 to 0.503)	<.001
12 SQ-HDM group	226	Mean (SD): 0.540 (0.026)	MD (95% CI): 0.595 (0.543 to 0.646)	<.001
Improvement in ACQ score controlled for ICS[e,f]				
Placebo group	277	No. (estimate in %): 218 (78.88)	Reference	
6 SQ-HDM group	275	No. (estimate in %): 221 (80.63)	OR (95% CI): 1.12 (0.73 to 1.70)	ND
12 SQ-HDM group	282	No. (estimate in %): 232 (83.02)	OR (95% CI): 1.31 (0.85 to 2.01)	.22
Improvement in AQLQ(S) score controlled for ICS[e,f]				
Placebo group	277	No. (estimate in %): 233 (84.80)	Reference	
6 SQ-HDM group	275	No. (estimate in %): 231 (84.98)	OR (95% CI): 1.01 (0.63 to 1.62)	ND
12 SQ-HDM group	282	No. (estimate in %): 236 (84.39)	OR (95% CI): 0.97 (0.61 to 1.53)	.89
Exploratory End Points				
Time to first asthma exacerbation with increased use of SABA				
Placebo group	257	32 (12)	Reference	
6 SQ-HDM group	237	23 (10)	0.62 (0.36 to 1.07)	.09
12 SQ-HDM group	248	18 (7)	0.52 (0.29 to 0.94)	.03
Time to first asthma exacerbation with deterioration in lung function				
Placebo group	257	45 (18)	Reference	
6 SQ-HDM group	237	31 (13)	0.60 (0.38 to 0.95)	.03
12 SQ-HDM group	248	30 (12)	0.58 (0.36 to 0.93)	.02

(continued)

Table 2. Overview of Primary, Key Secondary, and Exploratory End Point Efficacy Results for Each Treatment Group (continued)

End Point	Total Participants	No. of Participants With Event	Treatment Effect HR (95% CI)	*P* Value
Time to first severe asthma exacerbation				
Placebo group	257	18 (7)	Reference	
6 SQ-HDM group	237	17 (7)	0.79 (0.40 to 1.55)	.49
12 SQ-HDM group	248	10 (4)	0.49 (0.23 to 1.08)	.08

Abbreviations: ACQ, asthma control questionnaire; AQLQ(S), asthma quality of life questionnaire; FAS-MI, full analysis set with multiple imputation of missing data; HR, hazard ratio; MD, mean difference; NA, not applicable; ND, not done as per the hierarchical testing plan; OR, odds ratio.

[a] Period 3 was the start of the ICS reduction/withdrawal period (global null hypothesis [placebo = 6 SQ-HDM = 12 SQ-HDM; P = .047]).

[b] The number of participants with imputed data was 20 (7%) participants in the placebo group, 38 (14%) in the 6 SQ-HDM group, and 34 (12%) in the 12 SQ-HDM group.

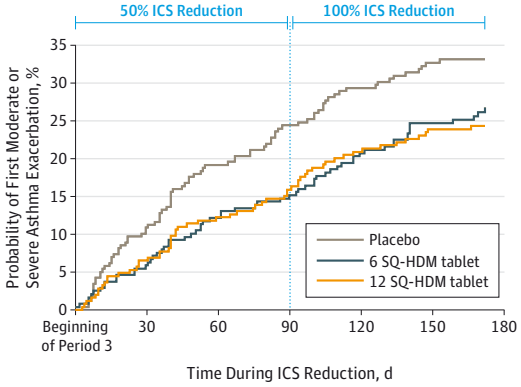
[c] In FAS-MI, the number of participants with first exacerbation is not applicable due to the imputation, in which participants who discontinued the study during period 2 were included as sampled from the placebo distribution of time to first asthma exacerbation during period 3.

[d] The absolute risk differences compared with the placebo group were 0.09 (95% CI, 0.01-0.15) for the 6 SQ-HDM group and 0.10 (95% CI, 0.02-0.16) for the 12 SQ-HDM group.

[e] Improvement in ACQ and AQLQ(S) score was defined as a change from baseline of more than 0.5 (ie, the established minimal important difference[23,24]). The odds ratio, 95% CI, and *P* value relate to the proportions with improvement.

[f] Estimate in percentage is based on the linear mixed-effect model with treatment group, baseline value as fixed effects and country as a random effect.

Figure 2. Probability of Having the First Moderate or Severe Asthma Exacerbation in the Full Analysis Set



No. at risk							
Placebo	257	228	200	188	171	163	109
6 SQ-HDM tablet	237	224	207	201	187	171	122
12 SQ-HDM tablet	248	228	214	207	189	180	121

ICS indicates inhaled corticosteroid. The biological activity of the house dust mite sublingual allergen immunotherapy tablet is related to the activity of the allergens and is expressed in the unit SQ-HDM. At the end of the 6-month efficacy assessment period, the 6 SQ-HDM and 12 SQ-HDM tablets significantly reduced the risk of a moderate or severe asthma exacerbation compared with placebo (hazard ratios: 0.69 [95% CI, 0.49-0.96] for the 6 SQ-HDM group, *P* = .03, and 0.66 [95% CI, 0.47-0.93] for the 12 SQ-HDM group, *P* = .02; absolute risk for first exacerbation: 24% for the 6 SQ-HDM group [n = 62], 24% for the 12 SQ-HDM group [n = 59], 33% for the placebo group [n = 83]; risk difference vs placebo: 9% [95% CI, 1%-15%] for the 6 SQ-HDM group and 10% [95% CI, 2%-16%] for the 12 SQ-HDM group). There was no significant difference between the 2 active groups (hazard ratio, 0.96 [95% CI, 0.68-1.37], *P* = .84).

The analyses of the odds for improvement in ACQ or AQLQ(S) score without an increased dose of ICS (third and fourth key secondary outcomes) showed no statistically significant differences between active treatment and placebo (ACQ score odds ratio [OR]: 1.12 [95% CI, 0.73-1.70] for the 6 SQ-HDM group vs placebo group and 1.31 [95% CI, 0.85-2.01] for the 12 SQ-HDM group vs placebo group; AQLQ(S) score OR: 1.01 [95% CI, 0.63-1.62] for the 6 SQ-HDM group vs placebo group and 0.97 [95% CI, 0.61-1.53] for the 12 SQ-HDM group vs placebo group) (Table 2).

Overall, 599 participants (72%) reported adverse events in a dose-dependent manner with the majority of all adverse events being mild (eTable 2 in Supplement 2). There was a dose-dependent change in the numbers of participants with treatment-related adverse events (39% from the 6 SQ-HDM group, 46% from the 12 SQ-HDM group, and 17% from the placebo group). The 3 most frequently reported adverse events were oral pruritus, mouth edema, and throat irritation (**Table 3**). The most common adverse events had a median onset time on day 1 or 2 after start of the treatment. The median onset in minutes on day 1 was 1 to 2 minutes. The median number of days from start of the adverse event until the event no longer occurred was 4.5 days for oral pruritus, 7 days for throat irritation, and 23 days for mouth edema. There were no safety findings of clinical concern in the subgroup with asthma classified as uncontrolled according to GINA.

No deaths occurred during the trial and there were no anaphylactic reactions, severe systemic allergic reactions, adverse events requiring epinephrine, or local allergic reactions compromising the airways. Twenty-eight participants reported 32 serious adverse events of which 5 were assessed as possibly treatment-related (for placebo [2 participants]: erosive esophagitis, hepatocellular injury; for 6 SQ-HDM tablet [2 participants]: arthralgia, laryngeal edema [moderate, no airway obstruction or dyspnea]; and for 12 SQ-HDM tablet [1 participant]: asthma [moderate, alternative etiology was "recently viral infection"]). There were no clinically relevant findings from clinical safety laboratory tests, physical examinations or vital signs.

Discussion

HDM is the most common allergen associated with asthma and more than 40% of adult asthmatics are atopic with a positive skin prick test result for the HDM allergens.[26,27] Although many

Table 3. Most Common Treatment-Related Adverse Events for Each Treatment Group Among Participants With HDM–Related Asthma

	Placebo Group (n = 277)		6 SQ-HDM Group (n = 275)[a]		12 SQ-HDM Group (n = 282)[a,b]	
	No. of Patients With Events (%)	No. of Events	No. of Patients With Events (%)	No. of Events	No. of Patients With Events (%)	No. of Events
All treatment-related adverse events	48 (17)	69	107 (39)	247	130 (46)	351
Gastrointestinal disorders	0	0	0	0	0	0
Oral pruritus	8 (3)	8	37 (13)	45	55 (20)	78
Edema mouth	0	0	24 (9)	26	28 (10)	35
Tongue pruritus	1 (<1)	1	12 (4)	13	13 (5)	15
Oral paresthesia	0	0	15 (5)	20	12 (4)	15
Lip edema	0	0	3 (1)	3	9 (3)	10
Nausea	0	0	0	0	8 (3)	8
Lip pruritus	0	0	0	0	7 (2)	8
Lip swelling	0	0	4 (1)	4	6 (2)	7
Swollen tongue	0	0	1 (<1)	1	5 (2)	6
Respiratory, thoracic, and mediastinal disorders	0	0	0	0	0	0
Throat irritation	4 (1)	4	21 (8)	26	27 (10)	32
Pharyngeal edema	0	0	0	0	5 (2)	6
Ear and labyrinth disorders	0	0	0	0		0
Ear pruritus	2 (<1)	2	7 (3)	7	11 (4)	11
Injury, poisoning, and procedural complications	0	0	0	0	0	0
Accidental overdose	9 (3)	12	4 (1)	5	15 (5)	16

Abbreviation: HDM, house dust mite.

[a] The biological activity of the house dust mite sublingual allergen immunotherapy tablet is related to the activity of the allergens and is expressed in the unit SQ-HDM.

[b] Adverse events occurred in less than 1% of the 12 SQ-HDM group.

patients with persistent asthma symptoms can be successfully treated with anti-asthmatic controller therapy including ICS, a significant proportion of patients remain uncontrolled.[5]

To our knowledge, this is the first controlled trial to show that adult patients with HDM allergy–related asthma who were not well controlled taking ICS can achieve an improvement in asthma control as measured by time to first asthma exacerbation with a sublingual tablet formulation of HDM allergen immunotherapy. The trial showed an HR for the FAS-MI of 0.69 [95% CI, 0.50-0.96] (absolute risk difference for a moderate to severe asthma exacerbation: 0.10 [95% CI, 0.02-0.16]) in the 12 SQ-HDM group vs placebo group during the ICS reduction period. For the 12 SQ-HDM group both the FAS-MI and FAS results for the primary analysis met this prespecified effect size. Thus, the HDM SLIT tablet has been shown to be effective in HDM allergy–related asthma both among patients well controlled adhering to GINA treatment steps 1 through 3,[12,13] as well as among patients not well controlled adhering to GINA treatment steps 2 through 4 at inclusion. Together, the data confirm an effect on both current asthma control and future risk.

Limitations of this trial include the operational definition of a moderate asthma exacerbation that, to our knowledge, was used for the first time. Although being applicable to a trial setting, the establishment of a baseline and the twice daily diary recordings will have limited usability in clinical practice. Also the specific selection of patients within a set range of ICS use and asthma control may pose a limitation. The trial had a shorter duration than a standard course of immunotherapy (often 3 years), which limits the conclusions on sustained effect. Furthermore, because the ultimate aim of allergen immunotherapy is disease-modification beyond the duration of treatment, a follow-up after the end of treatment would have been relevant. Additionally, the trial was not powered for comparative assessment of adverse events.

Although all patients had a positive skin prick test result for the HDM allergens, 66% of the participants had sensitizations to additional allergens included in the skin prick test panel. There was no difference, however, in the response to treatment with HDM SLIT tablet between patients sensitized to HDM only and patients with additional sensitizations, suggesting the HDM SLIT tablet was effective irrespective of patients being monosensitized or polysensitized.

The investigation of the effect on asthma exacerbations during ICS reduction is a new patient-relevant primary end point for allergen immunotherapy trials. Trials with asthma controller medication evaluating exacerbations in asthma have largely focused on severe exacerbations[28,29]; however, the aim in this trial was deliberately to detect asthma exacerbations and intervene before they developed into severe events. The concept of a moderate exacerbation has clinical utility, as early recognition of exacerbations may prevent patients from developing severe exacerbations, which ultimately can be life-threatening. We found that the ATS/ERS asthma exacerbation definition[20] (moderate and severe

exacerbations) was a sensitive primary trial outcome in this trial design. The measurement of time-to-first exacerbation was also recommended by the ATS/ERS joint task force report.[20] Previous trials with HDM allergen immunotherapy have focused on ICS reduction, asthma symptom scores, or lung function as primary end points with varying success.[30-32] In this trial, the intervention was added to standard anti-inflammatory treatment of asthma. The fact that the HDM SLIT tablet prevented asthma exacerbations when ICS was reduced could indicate an anti-inflammatory action of the active treatment that maintains the level of asthma control even in the absence of ICS. Efficacy was assessed in all asthma exacerbations in general as opposed to exacerbations induced by HDM exposure specifically. Furthermore, the treatment effect was evident in the primary end point and in a number of key and exploratory secondary end points, including immunological parameters.

The HDM SLIT tablet induced allergen-specific immunological changes typically associated with allergen immunotherapy (key secondary end point). This is supportive of the current assumption that the therapeutic effect is related to modulation of the immunological response to the allergen.[33-35]

The third and fourth key secondary end points, ACQ and AQLQ(S) score adjusted for ICS use, were novel attempts to make composite end points evaluating simultaneously the MID change from baseline in ACQ and AQLQ(S) score and change from baseline in ICS. It was found that 79% to 85% of participants improved in both the ACQ and AQLQ(S) scores with no differences between groups, including the placebo group. Thus the active treatment did not provide added benefit for these composite end points with patient-centered outcomes. The continuous improvement in ACQ and AQLQ(S) score adjusted for ICS use over time was seen even following ICS withdrawal, which was unexpected.

Severe and uncontrolled asthma has been known to constitute a risk in allergen immunotherapy. Therefore, participants with an FEV_1 lower than 70% of predicted value at randomization and participants with an asthma exacerbation leading to hospitalization within the last 3 months prior to randomization were excluded from the trial. During the entire trial, the participant's asthma status was carefully monitored. There was a dose-dependent change in the numbers of participants with treatment-related adverse events; primarily mild to moderate local reactions that lasted for some minutes after each tablet intake for the first days to weeks. The safety findings from this trial are similar to previous trials with the HDM SLIT tablet.[12-15]

Based on a cost-minimization analysis using a Danish setting as an example, the total treatment costs, including only direct costs, of a 3-year treatment with the HDM SLIT tablet is €3089 (approximately US $3400).[36]

Conclusions

Among adults with HDM allergy–related asthma not well controlled by ICS, the addition of HDM SLIT to maintenance medications improved time to first moderate or severe asthma exacerbation during ICS reduction, with estimated absolute reduction at 6 months of 9 to 10 percentage points; the reduction was primarily due to an effect on moderate exacerbations. Treatment-related adverse events were common at both active doses. Further studies are needed to assess long-term efficacy and safety.

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